REMARKS

Claims 1-4, 10, 16, 19 and 21 are pending in this application. Claims 2 and 3 are hereby canceled without prejudice to pursuing these claims in a continuing application. Claims 1, 4, 10, 16 and 19 are hereby amended. Upon entry of these amendments, claims 1, 4, 10, 16, 19 and 21 are pending and under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Applicant amends claim 1 to specify that the claimed transgenic mouse "is isolated" and "has at least one atrioventricular septal defect." Applicant amends claim 4 to maintain proper claim dependency. Claims 10, 16 and 19 are amended to delete reference to "phenotypes associated with" an atrioventricular septal defect. Support for amended claim 1 may be found in claim 3 of the specification as filed. Accordingly, Applicant respectfully submits that no new matter has been added.

I. Patentability Arguments

A. The Enablement Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

At page 3 of the Final Office Action, the Examiner maintains the rejection of claim19 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. Specifically, the Examiner alleges that one of ordinary skill in the art "would not know than [sic] any embryo tested has AVSD before being contacted with the agent" and therefore "the embryo may be one that did not have AVSD to start with."

Applicant respectfully points out to the Examiner that claim 19 is directed to a method for identifying a modulator of the development of atrioventricular septal defects (AVSDs). In order to identify a modulator of the development of AVSDs, a plurality of transgenic mouse embryos each comprising a heterozygous disruption the *CCN1* gene ($CCN1^{+/-}$ embryos) must be contacted with a suspected modulator prior to development of AVSD. Once an AVSD has developed and the phenotype determined, it is too late to screen for a modulator of the development of AVSD, as AVSD has already developed.

According to the Examiner, in order to be enabling, "the specification would need to describe examples that specifically address the in vivo determination of the phenotype for the same embryo or its progeny before and after contacting them with the test substance." *See* Final Office Action, page 5. Applicant submits that a modulator of the development of AVSD cannot be identified by serial phenotype measurements performed on the same embryo. The specification discloses that 35% of *CCN1*$^{+/-}$ mice do not display an AVSD phenotype by E14.5. Accordingly, contacting a *CCN1*$^{+/-}$ embryo with a suspected modulator of the development of AVSD prior to the development of AVSD, say at E10, yields no useful information. If later phenotypic measurements on said mouse reveal an absence of AVSD, the skilled artisan has no way of ascertaining whether the phenotype has been altered by the suspected modulator or whether said mouse belongs to the 35% of *CCN1*$^{+/-}$ mice that do not display an AVSD phenotype. Similarly, if later phenotypic measurements reveal the presence of an AVSD, the skilled artisan cannot ascertain whether the phenotype has been altered by the suspected modulator (e.g., the mouse may have developed AVSD in response to the suspected modulator). In other words, following contact of a *CCN1*$^{+/-}$ mouse at, say E10, with a suspected modulator, it is impossible to attribute an AVSD phenotype, or lack thereof, to contact with the suspected modulator.

As noted above, the specification teaches that 65% of transgenic mouse embryos comprising a heterozygous disruption of the *CCN1* gene possess AVSDs of varying severity by E14.5, while 35% of *CCN1*$^{+/-}$ mouse embryos do not exhibit an AVSD phenotype. *See* specification, paragraph [0071]. This disclosure provides a baseline against which a modulator of the development of AVSD can be identified. Briefly, a plurality of *CCN1*$^{+/-}$ embryos are contacted with a suspected modulator of development of AVSDs prior to the formation of atrioventricular septal structures. The specification teaches that *CCN1*$^{+/-}$ embryos exhibited the following phenotypes associated with AVSDs: (1) interventricular septal defect, occurring at about E12.5; (2) isolated cleft mitral valves; and (3) atrial septation defect occuring from about E10.5. *See* specification, Example 2. Thus, a plurality of *CCN1*$^{+/-}$ embryos may be contacted with a suspected modulator of the development of AVSDs prior to E10.5. At E14.5, the embryos are sacrificed and histological analysis performed on the hearts in order to measure phenotypes associated with AVSDs, as described throughout Example 2. If the percentage of *CCN1*$^{+/-}$ embryos exhibiting at least one phenotype associated with AVSDs is less than or greater than

65%, a modulator of the development of AVSDs is identified. Thus, the specification enables one of ordinary skill in the art, without undue experimentation, to determine if a suspected modulator is capable of altering the phenotype of the embryos in question.

Finally, although Applicant maintains that a modulator of the development of an AVSD cannot be obtained through serial phenotype measurements on a single *CCN1*$^{+/-}$ embryo/mouse, Applicant respectfully disagrees with Examiner's allegation that such measurements were not feasible at the time the Application was filed, because, according to the Examiner, "the art discloses that the genetic mouse models for cardiovascular diseases are still awaiting for the development of suitable methods to characterize their phenotype." *See* Final Office Action, page 5. Contrary to the Examiner's assertion, methods of assessing cardiovascular phenotypes in an intact mouse were available at the time the instant Application was filed. Applicant directs the Examiner's attention to the Supplemental Information Disclosure Statement, filed herewith, listing Collins *et al.*, Physiol. Genomics 13:227-239 (2003) (hereinafter "Collins *et al.*") and Gui *et al.*, Pediatr. Res. 40:633-642 (1996) (hereinafter "Gui *et al.*"). Collins *et al.* and Gui *et al.* are not prior art with respect to the instant invention, but provide evidence that one of ordinary skill in the art was enabled to perform serial, noninvasive measurements on mice (and embryos) to detect phenotypes associated with AVSDs.

Collins *et al.* reviews the use of echocardiography for assessing the phenotype of transgenic mice displaying abnormalities in cardiac development. According to Collins *et al.*, "[t]wo dimensional and Doppler echocardiography have been recently used as effective, noninvasive tools for murine imaging" and "[e]valuation of cardiovascular performance in closed chest mice is feasible in a variety of murine models using echocardiographic imaging." See Collins *et al*, abstract. Collins *et al.* cites a variety of studies in which serial echocardiography was successfully used to evaluate the progression of cardiovascular phenotypes. *See* e.g., Collins *et al.*, page 229, second full paragraph and page 233, first full paragraph. Cardiovascular phenotypes associated with AVSDs are well known in the art and are disclosed by the instant Application, at e.g., paragraphs [0003]-[0010]. At paragraph [0009], the instant Application discloses that "[a]trioventricular defects can be detected by Doppler echocardiography." According to Collins *et al.*, "Doppler ultrasound techniques, which allow the noninvasive assessment of cardiac output multiple times per experiment and the ability to follow changes serially, have been used [to measure cardiac output in mice]".

In fact, Doppler echocardiography has been successfully used to evaluate embryonic mouse heart development as far back as 1996. *See* Gui *et al.*, abstract. In that study, Doppler echocardiography on 20 mouse embryos with trisomy 16 from E11 through E14 revealed inflow or outflow valvular regurgitation in 55% of the trisomy 21 embryos (compared to 0% of normal mouse embryos). *See* Gui *et al.*, abstract. Importantly, trisomy 16 mice "have a well-described cardiac phenotype that includes AVSDs." *See* instant Application, paragraph [0011]. Thus, one of ordinary skill in the art, without undue experimentation, could have performed serial, noninvasive measurements on *CCN1*$^{+/-}$ mice (and embryos) to detect phenotypes associated with AVSDs.

In view of the foregoing, Applicant respectfully submits that the rejection of claim 19 under 35 U.S.C. § 112, second paragraph, may be properly withdrawn and hereby requests the Examiner withdraw the rejection.

B. The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

At page 6 of the Final Office Action, the Examiner maintains the rejections of claims 10 and 16 under 35 U.S.C. § 102(b) as anticipated by Mo *et al.* (Mol. Cell. Biol., 2002, 22:8709-8720). The Examiner characterizes Mo *et al.* (on page 6 of the Office Action) as "teach[ing] a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome (sic) comprise heterozygous or homozygous disruptions of the CCN1 gene and testing the transgenic mice for their genotype." The Examiner alleges that AVSDs (or predisposition thereto) are inherent in transgenic mice comprising a heterozygous disruption in *CCN1*. *See* Final Office Action, page 7.

Claim 10 relates to a method of producing a mouse with an AVSD. Mo *et al.* characterizes transgenic mice comprising homozygous disruptions of the *CCN1* gene, yet contains no description of any cardiovascular defects. No attempt is made to characterize transgenic mice comprising heterozygous disruptions of *CCN1*. According to *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), "in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." (emphasis in original). Absent a disclosure that *CCN1*$^{+/-}$ mice have or are prone to cardiovascular defects, the skilled artisan has no motivation to test *CCN1*$^{+/-}$ mice for a phenotype

associated with AVSD. Consequently, neither a step wherein *CCN1*$^{+/-}$ mice are tested for a phenotype associated with an AVSD nor a step wherein the subset of said mice displaying said phenotype are identified necessarily flow from the teachings of Mo *et al.* The Examiner alleges, at page 7 of the Final Office Action that Mo *et al.* "teach (sic) analyzing β-galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry." However, the portion of Mo *et al.* cited by the Examiner to support this allegation simply provides evidence of the disruption of a *Cyr61* allele by the *lacZ* cassette: "[h]eterozygous *Cyr61*$^{+/-}$ mice expressed β-galactosidase in a manner that accurately recapitulates expression of the *Cyr61* gene, as judged by comparing β-galactosidase staining patterns with those from the localization of *Cyr61* mRNA..." *See* Mo *et al.*, page 8710, column 2, second paragraph. Further, Mo *et al.*, at the next paragraph, teaches that "*Cyr61* heterozygotes were viable and fertile" while the instant specification teaches that *Cyr61* heterozygotes do "not exhibit any apparent phenotype." (emphasis added). *See* specification, paragraph [0017]. Thus, Mo *et al.* fails to disclose either a step for "testing" a *CCN1*$^{+/-}$ mouse for the presence of an AVSD or "identifying" a *CCN1*$^{+/-}$ mouse that has an AVSD. In light of the foregoing, the reference fails to meet the standard for an inherent disclosure and cannot anticipate claim 10 under 35 U.S.C. § 102(b). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections of claim 10 under 35 U.S.C. § 102(b).

Claim 16 covers a method of identifying a mouse with an AVSD. As noted supra, Mo *et al.* fails to disclose (1) that transgenic mice heterozygous for disruptions of the *CCN1* gene display AVSD or (2) testing of said mice for an AVSD so that mice displaying an AVSD can be identified. Therefore, Applicant respectfully submits that the reference fails to meet any of the limitations of claim 16 and respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

C. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

At page 8 of the Final Office Action, the Examiner maintains the rejection of claim 21 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mo *et al.* in view of both Mah *et al.* (Genet Test, 1999, 3:157-172) and Ciarleglio *et al.* (J Clin Invest, 2003, 112:1280-1286). The Examiner characterizes Mo *et al.* as teaching "a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise heterozygous or

homozygous disruption of the CCN1 gene and testing the transgenic mice for their phenotype." *See* Final Office Action, page 8.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981 (CCPA 1974). Second, there must be a reasonable expectation of success. *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986). Finally, there must be some suggestion or motivation for one of ordinary skill in the art to modify the reference or to combine the reference teachings. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

Applicant submits that Examiner has failed to establish a *prima facie* case of obviousness because the prior art references cited by the Examiner fail, separately and in combination, to teach or suggest all the claim limitations. Specifically, the cited references fail to disclose that transgenic mice comprising a heterozygous disruption of the *CCN1* gene are prone to AVSDs. As noted *supra*, such disclosure is not inherent to Mo *et al.* One of ordinary skill in the art would not have been motivated by Mo *et al.* to test $CCN1^{+/-}$ mice for a phenotype associated with an AVSD in light of *Mo et al.*'s disclosure that $CCN1^{+/-}$ mice are "viable and fertile" and in light of Mo *et al.*'s failure to disclose any phenotype for $CCN1^{+/-}$ mice. Mah *et al.* and Ciarleglio *et al.* fail to correct this deficiency of Mo *et al.*

In view of the failure of Mo *et al.*, alone or in combination with Mah *et al.* and Ciarleglio *et al.*, to explicitly or inherently teach or suggest that transgenic mice comprising a heterozygous disruption of the *CCN1* gene are prone to AVSDs, Applicant respectfully submits that claim 21 is not obvious and thus requests reconsideration and withdrawal of the rejection to claim 21 under 35 U.S.C. § 103(a).

Further, Applicant submits that Examiner has failed to establish a *prima facie* case of obviousness because none of the prior art references cited by the Examiner provides a suggestion or motivation to modify or combine the references. Mo *et al.* contains no suggestion of a correlation between disruption of *CCN1* function and the development of AVSDs. In the absence of such a teaching, one of ordinary skill in the art would not have been motivated to combine the cited references. Nor does MO *et al.* provide any motivation for one of ordinary skill in the art to modify the disclosure. As noted *supra*, Mo et al. discloses that $CCN1^{+/-}$ mice

are "viable and fertile" and fails to explicitly or inherently disclose any phenotype for *CCN1*$^{+/-}$ mice. Mah *et al.* and Ciarleglio *et al.* fail to correct this deficiency of Mo *et al.*

In view of the failure of Mo *et al.* alone or in combination with Mah *et al.* and Ciarleglio *et al.* to provide a suggestion or motivation to modify or combine the references, Applicant respectfully submits that claim 21 is not obvious in view of Mo *et al.* in view of Mah *et al.* and Ciarleglio *et al.* and thus requests reconsideration and withdrawal of the rejection to this claim under 35 U.S.C. § 103(a).

D. The New Rejections Under 35 U.S.C. § 112, 1st Paragraph for Written Description and Enablement Should be Withdrawn

At pages 9-10 of the Final Office Action, the Examiner rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. The Examiner does not offer any basis for the enablement rejection aside from a conclusory statement that "a transgenic mouse comprising a suspected modulator of the development of atriovascular septal defects is not enabled by the disclosure." *See* Final Office Action, page 9. The Examiner offers as a basis for the written description rejection only the allegation that "the instant specification does not disclose a transgenic mouse comprising a suspected modulator of the development of atriovascular septal defects..." *See* Final Office Action, page 10.

Applicant respectfully disagrees with the Examiner's rejections and submits that the Examiner has failed to meet the burden required to establish rejections for an alleged lack of written description and an alleged lack of enablement as required under MPEP §§ 2163.04 and 2164.04, respectively. However, in the interest of expediting prosecution of the instant application, Applicant herein cancels claim 2-3 and amends claim 1 to delete reference to a suspected modulator of the development of atrioventricular septal defects. Applicant thus requests withdrawal of the rejections of claims 1-4 under 35 U.S.C. § 112, first paragraph.

E. The New Rejections Under 35 U.S.C. § 112, 2nd Paragraph Should Be Withdrawn

At page 10 of the Final Office Action, the Examiner rejects claims 1-4 under 35 U.S.C. § 112 as allegedly failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. In light of Applicant's cancellation of claims 2-3 and the amendment to

claim 1, the rejections are moot. Applicant therefore requests withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

F. The New Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

At page 10 of the Final Office Action, the Examiner rejects claims 1-4 under 35 U.S.C. 103(a) as allegedly unpatentable over Mo *et al.* in view of Lau *et al* (PGPUB 2004/0002124). The Examiner characterizes Mo *et al.* as teaching a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise a heterozygous disruption of the CCN1 gene, and testing the transgenic mice for their genotype." *See* Final Office Action, page 11. Further, the Examiner alleges that "the heterozygous disruption in the CCN1 gene must necessarily have resulted in the claimed AVSDs" and that "Mo et al. teach analyzing β-galactosidase expression in heterozygous mice…and this would necessarily have resulted in the determination of AVSD…" *See* Final Office Action, page 11.

Applicant cancels claims 2-3 and amends claim 1 to cover an "isolated" transgenic mouse comprising a heterozygous disruption in the *CCN1* gene wherein said mouse has at least one atrioventricular septal defect. Contrary to the Examiner's allegations, heterozygous disruption of the *CCN1* gene does not necessarily result in the claimed AVSDs. As noted *supra*, the instant specification discloses that 35% of *CCN1*$^{+/-}$ mice do not display an atrioventricular septal defect. Further, as noted *supra*, and contrary to Examiner's allegation, Mo *et al.* does not inherently disclose that *CCN1*$^{+/-}$ mice are prone to atrioventricular septal defects. Lau *et al.* fails to correct this deficiency. Thus, Mo *et al.*, alone or in combination with Lau *et al.*, fails to disclose an isolated *CCN1*$^{+/-}$ mouse wherein said mouse has an atrioventricular septal defect. Because the cited references, alone or in combination, fail to disclose each and every limitation of claim 1 and claim 4, which depends from claim 1, the claims are nonobvious.

The Examiner characterizes Lau *et al.* as teaching "transgenic mice comprising a heterozygous disruption of the *CCN1* gene, wherein the transgenic mice are useful as disease models." However, Lau *et al.* does not teach that *CCN1*$^{+/-}$ mice are prone to atrioventricular septal defects nor are *CCN1*$^{+/-}$ mice taught as potential disease models for atrioventricular septal defects. Further, at paragraph [0285], cited by the Examiner to support his allegation, Lau *et al.* states that "[h]eterozygous mice (cyr61+/-) appeared to be normal, as these mice did not exhibit any apparent phenotype." Thus, Lau *et al.* actually teaches away from the instant invention.

Accordingly, the cited references, alone or in combination, do not provide any suggestion or motivation to modify or combine the references.

In light of the foregoing, Applicant respectfully submits that one of ordinary skill in the art, prior to the inventive disclosure of the instant application, could not have isolated a *CCN1*$^{+/-}$ mouse with an atrioventricular septal defect. Accordingly, Applicant requests reconsideration and withdrawal of the rejections of claims 1-4 under 35 U.S.C. § 103(a).

II. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully submits that the claims are now in condition for allowance and early notification thereof is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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